Remarks

Applicants request consideration on the merits of the above-referenced patent application.

I. Amendments to the Claims

Claims 1-6, 8, 10, 12, 14, 15, 39-44, 46-52, and 57-61 are pending in this application. All pending claims are shown in the previous section.

II. Amendments to the Drawings

The Notice Regarding Drawings objects to figures 1-16. According to the Notice, figures 2, 4, 5, 7, 9-13, 15, and 16 have solid background, and all figures have unacceptable marks, margins, and poor line quality.

Applicants cannot file corrected drawings without solid black background by the July 31, 2004 deadline because they have been unable to locate the original color prints from which figures 2, 4, 5, 7, 9-13, 15, and 16 had been prepared. Thus, Applicants have canceled figures 2, 4, 5, 7, 9-13, 15, and 16. Applicants believe that the canceled figures are not necessary for the understanding of the subject matter of the allowed compound and method of use claims.

Applicants have renumbered figures 1, 3, 6, 8, and 14 as figures 1-5, respectively.

Applicants also have enclosed replacement figures. Applicants believe that those replacement figures comply with 37 C.F.R. §1.84.

III. Amendments to the Specification

Applicants have amended the specification to reflect the deletion of figures 2, 4, 5, 7, 9-13, 15, and 16. Applicants believe that the amendments to the specification do not introduce new matter.

Other amendments simply rephrase the specification, or correct grammatical or obvious errors. Applicants submit that such amendments are permissible under MPEP §2163.07.

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Applicants have enclosed a check for $900.00 to cover the fees for the request for continued examination and the petition under 37 C.F.R. §1.313(c)(2). Applicants do not believe

that they owe any other fee(s) in connection with this submission. If, however, Applicants do owe any fee(s), the Commissioner is hereby authorized to charge the fee(s) to Deposit Account No. **08-0750**. In addition, if there is ever any other fee deficiency or overpayment under 37 C.F.R. § 1.16 or § 1.17 in connection with this patent application, the commissioner is hereby authorized to charge such deficiency or overpayment to Deposit Account No. **08-0750**.

Applicants submit that the application is in condition for allowance, and request that it be allowed. Applicants also request that the Examiner call the Undersigned if any issues arise that can be addressed over the phone to expedite examination of this application.

Respectfully submitted,

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CERTIFICATE OF MAILING UNDER 37 C.F.R. 1.8

I certify that this correspondence is being deposited with the U.S. Postal Service on **July 31, 2004** with sufficient postage as first class mail (including Express Mail per MPEP § 512), and addressed to **Mail Stop Petition, Commissioner For Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.**

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LNN/PML

Appendix A
Marked-Up Version of Amendments to Specification

The paragraph bridging lines 5-7 on page 11 has been deleted.

The paragraph bridging lines 8-10 on page 11 has been amended as follows:

Figure **[[3]]** **2** shows MMP-8 S1' amino acid backbone residues which reside within 5 Å of a complexed inhibitor molecule.

The paragraph bridging lines 11-12 on page 11 has been deleted.

The paragraph bridging lines 13-16 on page 11 has been amended as follows:

Figures **[[5, 6, 7,]]** **3** and **4** **[[8]]** show the effect of progressively lengthening the P1' group of an MMP inhibitor on the conformation of the substituents on amino acid residues of the S1' pocket.

The paragraphs bridging lines 17-23 on page 11 have been deleted.

The paragraph bridging lines 24-25 on page 11 has been amended as follows:

Figure **[[14]]** **5** shows the (φ,ψ) distribution among the 25 amino acid residues of MMP-8 from 222 to 231.

The paragraph bridging lines 26-28 on page 11 has been deleted.

The paragraph bridging lines 6-19 on page 24 has been amended as follows:

The catalytic domain (residues 85-242) of MMP-8, neutrophil collagenase, folds into a compact globular structure. It has an approximate diameter of 30 Å. The inhibitors interact with the protein through chelation of the catalytic zinc ion, hydrogen bonding with the backbone -NH- of Leu 160, and hydrophobic interactions in the nonpolar S1' pocket. In MMP-8, the S1' pocket is formed from residues 193-197 that form a turn of a longer helix and residues 214-229 of a loop region. The S1' pocket in MMP-8 is not as deep as in some other MMPs (e.g., stromelysin).

~~The accompanying figures show the effect on the~~ The conformation of the S1' pocket changes as the P1' substituent on the inhibitor is made progressively longer.

The paragraph bridging pages 24 and 25 (*i.e.*, page 24, line 20 to page 25, line 8) has been amended as follows:

~~Figure 2 shows the structures of inhibitor molecules of Formulae XII, IX, X, and XI superimposed upon one another, wherein the structures were determined by the~~ X-ray crystallographic techniques described herein ~~. The Figure shows~~ showed the co-extensive reach of the P1' arms of the inhibitors XII, IX, X, and XI, except that as the alkyl group of the 4-alkylbenzamide moiety increases in length, the steric requirements of each inhibitor also increases. The P1' arm of each inhibitor fits into the MMP-8 S1' pocket. In order to accommodate an increase in the steric requirement of the P1' arm, the amino acid residues of the S1' pocket must change their conformations.

The paragraph bridging lines 9-16 on page 25 has been amended as follows:

Figure ~~[[3]]~~ 2 shows MMP-8 S1' amino acid backbone residues which reside within 5 Å of a complexed inhibitor molecule as determined by the X-ray crystallographic techniques described herein. A blank in Figure 3 indicates that the residue lies within 5 Å of the inhibitor whereas the word "no" indicates that the residue lies further than 5 Å from the complexed inhibitor.

The paragraphs bridging lines 17-22 on page 25 have been deleted.

The paragraph bridging lines 23-34 on page 25 has been amended as follows:

~~Figure 5 shows a comparison of the~~ X-ray crystallography ~~crystallographic conformation of amino acid residues in the S1' pocket of MMP-8 when either the~~ of the complex of the compound of Formula XII ~~(colored)~~ or the compound of Formula XIV ~~(grey) is complexed~~ with MMP-8 ~~. The figure shows~~ showed that the P1' group (including the 4-propylbenzamide moiety) of compound XII sterically interferes with the side chain of the Arg 222 (R222) residue of the S1' pocket of MMP-8, while the P1' group of compound XIV is much

shorter and does not sterically interfere with the Arg 222 **[[the]]** side chain. Complexed **compound** XII causes the Arg 222 **[[the]]** side chain to move out of the way of the large P1' group of XII.

The paragraph bridging pages 25 and 26 (*i.e.*, page 25, line 35 to page 26, line 9) has been amended as follows:

Figure **[[6]] 3** shows a comparison of the X-ray crystallographic conformation of amino acid residues in the S1' pocket of MMP-8 when either the compound of Formula XII ~~**(colored)**~~ **(black)** or the compound of Formula IX (grey) is complexed with MMP-8. The P1' group of **compound** IX (including the 4-pentylbenzamide moiety) is larger still than the P1' group of **compound** XII. Because of increased steric interference, the **[[IX]]** P1' group **of compound IX** causes the **[[the]]** side chain of the Arg 222 (R222) residue of the S1' pocket **of MMP-8** to move even further away from the pocket than does the P1' group of **compound** XII.

The paragraph bridging lines 10-20 on page 26 has been amended as follows:

~~**Figure 7 shows a comparison of the X-ray crystallographic conformation of amino acid residues in the S1' pocket of MMP-8 when either the compound of Formula XII (colored) or the compound of Formula X (grey) is complexed with MMP-8.**~~ The P1' group of X (including the 4-hexylbenzamide moiety) is larger still than the P1' group of XII. ~~**Because of**~~ **X-ray crystallography showed that, due to** increased steric interference, the P1' group of **compound** X causes the side chain of the Arg 222 (R222) residue of the S1' pocket **of MMP-8** to move as far or further away from the pocket than does the XII P1' group.

The paragraph bridging lines 21-26 on page 26 has been amended as follows:

Figure **[[8]] 4** shows a comparison of the X-ray crystallographic conformation of amino acid residues in the S1' pocket of MMP-8 when either the compound of Formula XII ~~**(colored)**~~ **(black)** or the compound of Formula XI (grey) is complexed with MMP-8. This Figure shows a result similar **to the comparison between compounds XII and X** ~~**that of Figure 7**~~.

The paragraph bridging lines 27-30 on page 26 has been deleted.

The paragraph bridging pages 26 and 27 (*i.e.*, page 26, line 31 to page 27, line 6) has been amended as follows:

~~**Figure 9 shows a comparison of the**~~ X-ray **crystallography** ~~**crystallographic conformation**~~ of the amino acid backbone of the S1' pocket of MMP-8 when either the compound of Formula XII ~~**(green)**~~ or the compound of Formula XIV ~~**(red)**~~ is complexed with MMP-8 **showed** ~~**. Although Figure 9 demonstrates**~~ that **compound** XII affects the conformation of the side chain of the Arg 222 (R222) residue of the Sl' pocket relative to **compound** XIV**.** **[[, Figure 9]]** **It** also ~~**shows**~~ **showed** that each compound has essentially no effect on the conformation of the amino acid backbone ~~*(shown as a ribbon in Figure 9)*~~. Tyr 227 (Y227) shows little change when either **compound** XII or XIV is complexed in the S1' pocket.

The paragraph bridging lines 6-16 on page 27 has been amended as follows:

~~**Figure 10 shows a comparison of the**~~ X-ray **crystallography** ~~**crystallographic conformation**~~ of the amino acid backbone of the S1' pocket of MMP-8 when either the compound of Formula XII ~~**(red)**~~ or the compound of Formula X ~~**(yellow)**~~ is complexed with MMP-8 **showed that the** **[[. The]]** longer 4-pentylbenzamide moiety of **compound** X causes the backbone to deform significantly relative to the case in which **compound** XII is complexed. In addition, **compound** X causes the Arg 222 and Tyr 227 side chains to move significantly relative to the case in which **compound** XII is complexed.

The paragraph bridging lines 17-26 on page 27 has been amended as follows:

~~**Figure 11 shows a comparison of the**~~ X-ray **crystallography** ~~**crystallographic conformation**~~ of the amino acid backbone of the S1' pocket of MMP-8 when either the compound of Formula XII ~~**(red)**~~ or the compound of Formula IX ~~**(yellow)**~~ is complexed with MMP-8 **showed that the** **[[. The]]** longer 4-pentylbenzamide moiety of **compound** IX causes the backbone to deform significantly relative to the case in which **compound** XII is complexed. In addition, **compound** IX causes the Arg 222 and Tyr 227 side chains to move significantly relative to the case in which **compound** XII is complexed.

The paragraph bridging lines 27-36 on page 27 has been amended as follows:

~~**Figure 12 shows a comparison of the**~~ X-ray **crystallography** ~~**crystallographic conformation**~~ of the amino acid backbone of the S1' pocket of MMP-8 when either the compound of Formula XII ~~**(red)**~~ or the compound of Formula XI ~~**(blue)**~~ is complexed with MMP-8 **showed that the [[. The]]** longer 4-hexylbenzamide moiety of **compound** XI causes the backbone to deform significantly relative to the case in which **compound** XII is complexed. In addition, XI causes the Arg 222 and Tyr 227 side chains to move significantly relative to the case in which XII is complexed.

The paragraph bridging lines 1-11 on page 28 has been amended as follows:

~~**Figure 13 shows the temperature factor (B) distribution for MMP-8 complexes with inhibitor compounds XII (red), IX (orange), X (yellow), XI (blue), and XIV (white).**~~ Complexes **of MMP-8** with **compounds** XII and XIV show similar temperature factors indicating that the MMP-8 backbone has similar thermal motion in both cases. However, **MMP-8** complexes with **compounds** XI, X, and IX ~~**complexes**~~ cause a progressive increase in the temperature factor in residues 221-230, indicating that they are causing greater thermal motion in that region of the S1' pocket of MMP-8 relative to compounds X or XIV.

The paragraph bridging lines 12-13 on page 28 has been amended as follows:

Figure **[[14]] 5** shows the (φ,ψ) distribution among the amino acid residues of MMP-8 from 222 to 231.

The paragraph bridging lines 14-30 on page 28 has been amended as follows:

~~**Figure 15 shows an electrostatic surface of one aspect of the overall MMP-8 enzyme in which the inhibitor compound of Formula XIV has been complexed. Figure 16 shows an electrostatic surface of one aspect of the overall MMP-8 enzyme in which the inhibitor compound of Formula XI has been complexed. Figure 16 (center) shows**~~ **Comparison between the electrostatic surfaces of the MMP-8 complex with compounds XIV and XI showed** that **[[the]] compound** XI has caused a change in the conformation of MMP-8 relative to **compound** XIV as evidenced by the opening created by **compound** XI in the S1' pocket

caused by the change in conformation of the amino acid residue backbone of MMP-8. This opening is absent from the **compound** XIV-MMP-8 complex ~~**shown in Figure 15**~~. The electrostatic surfaces were calculated ~~**and drawing**~~ using the GRASP program (A. Nicholls et al., "Protein folding and association: Insights from the interfacial and thermodynamic properties of hydrocarbons," *Protein Str. Funct. Gen.* 11, 281-296 (1991)).

The paragraph bridging pages 28 and 29 (*i.e.*, page 28, line 31 to page 27, line 2) has been amended as follows:

~~**These figures demonstrate that stepwise**~~ **Stepwise** changes of the MMP-8 protein are observed in progressing from complexes of MMP-8 with XIV, XII, IX, X, and XI. The S1' pocket becomes deeper, first by the movement of amino acid residue side chains (especially Arg 222 and Tyr 227), then by a movement of the backbone in the 224-228 region.